132240

Shears, Beverly

From: Devi, Sarvamangala
Sent: Wednesday, September 08, 2004 1:41 PM
To: Shears, Beverly
Subject: 10/009,254

Beverly:

Would you please perform a sequence and an interference search for SEQ ID NO: 1.

Please include a search on inventors' names: Elisabeth E. Adderson and John F. Bohnsack.

Thanx.

S. DEVI, Ph.D.
AU 1645
Rems - 3C18

Date completed: 09-1
Searcher: Beverly e 2528
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Total time: _____
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Number of Databases: 3

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_____ Structure
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Vendors
_____ IG
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✓ Other CGN

PTO-1590 (9-90)

Deji, S.
10/009254

13sep04 10:25:57 User219783 Session D2045.2

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File 65:Inside Conferences 1993-2004/Sep W1
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Set Items Description
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_ Author(s)

Set	Items	Description
S1	94	AU=(ADDERSON, E? OR ADDERSON E?)
S2	169	AU=(BOHNSACK, J? OR BOHNSACK J?)
S3	35	S1 AND S2
S4	17	(S1 OR S2 OR S3) AND AGALACTIAE
S5	11	RD (unique items)
S6	11	S5 AND (GBS OR GROUP(W)B)

>>>No matching display code(s) found in file(s): 65, 113

6/3,AB/1 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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19034154 Document Delivery Available: 000223153200009 References: 22
TITLE: Serotype III Streptococcus **agalactiae** from bovine milk and human neonatal infections
AUTHOR(S): **Bohnsack JF (REPRINT)**; Whiting AA; Martinez G; Jones N; **Adderson EE**; Detrick S; Blaschke-Bonkowsky AJ; Bisharat N; Gottschalk M
AUTHOR(S) E-MAIL: john.bohnsack@hsc.utah.edu
CORPORATE SOURCE: Univ Utah, Dept Pediat, 50 N Med Dr/Salt Lake City//UT/84132 (REPRINT); Univ Utah, Dept Pediat, /Salt Lake City//UT/84132; Univ Montreal, Fac Med Vet, /St Hyacinthe/PQ J2S 7C6/Canada/; John Radcliffe Hosp, /Oxford OX3 9DU//England/; St Jude Childrens Hosp, /Memphis//TN/38105
PUBLICATION TYPE: JOURNAL
PUBLICATION: EMERGING INFECTIOUS DISEASES, 2004, V10, N8 (AUG), P1412-1419
GENUINE ARTICLE#: 844JC
PUBLISHER: CENTER DISEASE CONTROL, ATLANTA, GA 30333 USA
ISSN: 1080-6040
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Streptococcus **agalactiae** (**group B** streptococcus [**GBS**]) causes invasive human infections and bovine mastitis. This study examined the genetic relationship between bovine and human serotype III **GBS** by using molecular techniques that classify human serotype III **GBS** into four distinct phylogenetic lineages. Bovine serotype III **GBS** were largely contained in two lineages, which are distinct from the two major lineages (restriction digest types III-2 and III-3) that

infect human neonates. One of the bovine lineages closely resembles the human III-1 lineage, whose members occasionally cause human neonatal infections. The bovine strains in the other lineage characteristically have an initiation factor IF2 gene (infB) H allele and multilocus sequence types that are not found in human **GBS** strains. Evidence suggests that this "H allele" lineage is related to the human III-3 lineage. These results support the assertion that human and bovine **GBS** are largely unrelated and provide further insight into the genetic relation between human and bovine **GBS**.

6/3,AB/2 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

18686128 Document Delivery Available: 000221981000006 References: 19
TITLE: Equivalence of high-virulence clonotypes of serotype III **group B** Streptococcus **agalactiae** (**GBS**)
AUTHOR(S): Fleming KE; **Bohnsack JF**; Palacios GC; Takahashi S; **Adderson EE (REPRINT)**
AUTHOR(S) E-MAIL: Elisabeth.Adderson@stjude.org
CORPORATE SOURCE: St Jude Childrens Hosp, Dept Infect Dis, 332 N Lauderdale St/Memphis//TN/38105 (REPRINT); St Jude Childrens Hosp, Dept Infect Dis, /Memphis//TN/38105; Univ Utah, Dept Pediat, /Salt Lake City//UT/; Univ Utah, Dept Pathol, /Salt Lake City//UT/; Inst Mexicano Seguro Social, /Mexico City/DF/Mexico/; Joshi Eiyoh Univ, Dept Microbiol, /Sakano//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF MEDICAL MICROBIOLOGY, 2004, V53, N6 (JUN), P505-508
GENUINE ARTICLE#: 828NW
PUBLISHER: SOC GENERAL MICROBIOLOGY, MARLBOROUGH HOUSE, BASINGSTOKE RD, SPENCERS WOODS, READING RG7 1AG, BERKS, ENGLAND
ISSN: 0022-2615
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Analysis of growth characteristics, multilocus enzyme electrophoresis, restriction digest pattern (RDP) typing and multilocus sequence typing have identified clonotypes of serotype III **group B** Streptococcus **agalactiae** (GIBS) associated with invasive infection in neonates. This study sought to unify phenotypic and genotypic classifications of type III **GBS** strains associated with increased virulence in newborns. High-virulence clonotype (HVC) strains possessed the translation initiation factor 2 (infB) C allele, found in RDP type III-3 strains, and hybridized with the RDP type III-3-specific probe AA3.6, whereas non-HVC strains shared the infB A allele and genomic DNA from these strains did not hybridize with the AA3.6 probe. The characteristic growth lag of HVC **GBS** at 40degreesC has been attributed to the presence of a heat-labile fructose-1,6-bisphosphate aldolase (Fba) enzyme in these strains. The deduced amino acid sequence of fba genes of both HVC and non-HVC strains, however, were identical. HVC and RDP type III-3 represent the same genetically related group of bacteria. The characteristic growth differences of virulent strains of type III GIBS, however, are not directly attributable to differences in fba.

6/3,AB/3 (Item 3 from file: 440)

DIALOG(R)File 440:Current Contents Search(R)

17409452 Document Delivery Available: 000186835500023 References: 38
TITLE: Subtractive hybridization identifies a novel predicted protein mediating epithelial cell invasion by virulent serotype III **group B** Streptococcus **agalactiae**
AUTHOR(S): **Adderson EE (REPRINT)**; Takahashi S; Wang Y; Armstrong J; Miller DV; **Bohnsack JF**
AUTHOR(S) E-MAIL: Elisabeth.Adderson@stjude.org
CORPORATE SOURCE: St Jude Childrens Hosp, Dept Infect Dis, Rm E8054,Mailstop 320,332 N Lauderdale St/Memphis//TN/38105 (REPRINT); St Jude Childrens Hosp, Dept Infect Dis, /Memphis//TN/38105; Joshi Eiyoh Univ, Chiyoda Ku, /Sakado/Saitama 3500288/Japan/; Univ Utah, Dept Pediat, /Salt Lake City//UT/84132; Univ Utah, Dept Pathol, /Salt Lake City//UT/84132
PUBLICATION TYPE: JOURNAL
PUBLICATION: INFECTION AND IMMUNITY, 2003, V71, N12 (DEC), P6857-6863
GENUINE ARTICLE#: 747ZA
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0019-9567
LANGUAGE: English DOCUMENT TYPE: ARTICLE
ABSTRACT: **Group B** Streptococcus **agalactiae** bacteria (**group B** streptococci [**GBS**]) are the most common cause of serious bacterial infection in newborn infants. The majority of serotype III-related cases of neonatal disease are caused by a genetically related subgroup of bacteria, restriction fragment digest pattern (RDP) type III-3, suggesting that these strains possess unique genes contributing to virulence. We used genomic subtractive hybridization to identify regions of genomic DNA unique to virulent RDP type III-3 **GBS** strains. Within one of these III-3-specific regions is a 1,506-bp open reading frame, spb1 (surface protein of **group B** streptococcus 1). A mutant type III **GBS** strain lacking Spb1 was constructed in virulent RDP type III-3 strain 874391, and the interactions of the wild-type and spb1 isogenic mutant with a variety of epithelial cells important to **GBS** colonization and infection were compared. While adherence of the spb1 isogenic mutant to A549 respiratory, C2Bbe1 colonic, and HeLa cervical epithelial cells was slightly lower than that of the 874391 strain, invasion of the Spb1(-) mutant was significantly reduced with these cell lines compared to what was seen with 874391. The defect in epithelial invasion was corrected by supplying spb1 in trans. These observations suggest that Spb1 contributes to the pathogenesis of neonatal **GBS** infection by mediating internalization of virulent serotype III **GBS** and confirm that understanding of the population structure of bacteria may lead to insights into the pathogenesis of human infections.

6/3,AB/4 (Item 4 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

16398382 Document Delivery Available: 000183466200043 References: 26
TITLE: Multilocus sequence typing system for **group B** streptococcus
AUTHOR(S): Jones N (REPRINT); **Bohnsack JF**; Takahashi S; Oliver KA;

Chan MS; Kunst F; Glaser P; Rusniok C; Crook DWM; Harding RM; Bisharat N; Spratt BG
AUTHOR(S) E-MAIL: nicola.jones@ndcls.ox.ac.uk
CORPORATE SOURCE: John Radcliffe Hosp, Nuffield Dept Clin Lab Sci, Level 7/Oxford OX3 9DU//England/ (REPRINT); John Radcliffe Hosp, Nuffield Dept Clin Lab Sci, /Oxford OX3 9DU//England/; John Radcliffe Hosp, Inst Mol Med, /Oxford OX3 9DU//England/; Univ Oxford, /Oxford OX1 3SY//England/; Univ London Imperial Coll Sci Technol & Med, Dept Infect Dis Epidemiol, /London W2 1PG//England/; Univ Utah, Dept Pediat, /Salt Lake City//UT/84132; Joshi Eiyoh Univ, Div Microbiol, /Sakado/Saitama 3500288/Japan/; Inst Pasteur, Lab Genom Microorganismes Pathogenes, /F-75724 Paris 15//France/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF CLINICAL MICROBIOLOGY, 2003, V41, N6 (JUN), P 2530-2536
GENUINE ARTICLE#: 688ZB
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0095-1137
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: A multilocus sequence typing (MLST) system was developed for **group B** streptococcus (**GBS**). The system was used to characterize a collection (n = 152) of globally and ecologically diverse human strains of **GBS** that included representatives of capsular serotypes la, Ib, 11, 111, V, VI, and VIII. Fragments (459 to 519 bp) of seven housekeeping genes were amplified by PCR for each strain and sequenced. The combination of alleles at the seven loci provided an allelic profile or sequence type (ST) for each strain. A subset of the strains were characterized by restriction digest patterning, and these results were highly congruent with those obtained with MLST. There were 29 STs, but 66% of isolates were assigned to four major STs. ST-1 and ST-19 were significantly associated with asymptomatic carriage, whereas ST-23 included both carried and invasive strains. All 44 isolates of ST-17 were serotype III clones, and this ST appeared to define a homogeneous clone that was strongly associated with neonatal invasive infections. The finding that isolates with different capsular serotypes had the same ST suggests that recombination occurs at the capsular locus. A web site for **GBS** MLST was set up and can be accessed at http://sagalactiae.mlst.net. The **GBS** MLST system offers investigators a valuable typing tool that will promote further investigation of the population biology of this organism.

6/3,AB/5 (Item 5 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

14657185 Document Delivery Available: 000177991100021 References: 15
TITLE: Correlation of phylogenetic lineages of **group B** streptococci, identified by analysis of restriction-digestion patterns of genomic DNA, with infB alleles and mobile genetic elements
AUTHOR(S): Takahashi S; Detrick S; Whiting AA; Blaschke-Bonkowksy AJ; Aoyagi Y; **Adderson EE; Bohnsack JF (REPRINT)**
AUTHOR(S) E-MAIL: john.bohnsack@hsc.utah.edu
CORPORATE SOURCE: Univ Utah, Dept Pediat, 50 N Med Dr/Salt Lake City//UT/84132 (REPRINT); Univ Utah, Dept Pediat, /Salt Lake

City//UT/84132; Joshi Eiyoh Univ, Chiyoda Ku, /Sakado/Saitama/Japan/; Univ Utah, Dept Pathol, /Salt Lake City//UT/84132; St Jude Childrens Hosp, Dept Infect Dis, /Memphis//TN/38105
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF INFECTIOUS DISEASES, 2002, V186, N7 (OCT 1), P 1034-1038
GENUINE ARTICLE#: 593KU
PUBLISHER: UNIV CHICAGO PRESS, 1427 E 60TH ST, CHICAGO, IL 60637-2954 USA
ISSN: 0022-1899
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Phylogenetic lineages of pathogenic Streptococcus **agalactiae** (**group B** streptococci [**GBS**]) can be identified by analysis of restriction-digestion patterns (RDPs) of chromosomal DNA. The purpose of the present study was to correlate **GBS** RDP types and (1) alleles of the highly conserved gene encoding translation-initiation factor IF2, infB, and/or (2) the inserted elements IS1548 and GBSi1. Only 1 combination of serotype and infB allele was found within each RDP type. Strains within a particular RDP type also tend to have the same inserted elements in each of 3 loci examined. A novel insertion sequence, designated "IS1563," was found within all RDP type II-2 strains. Most RDP types could be identified by a combination of serotype, infB allele, and inserted elements at each of the loci. These molecular markers can be used to identify **GBS** populations and to correlate RDP types and phylogenetic lineages identified by different methods.

6/3,AB/6 (Item 6 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

13349826 References: 23
TITLE: Long-range mapping of the Streptococcus **agalactiae** phylogenetic lineage restriction digest pattern type III-3 reveals clustering of virulence genes
AUTHOR(S): **Bohnsack JF (REPRINT)**; Whiting AA; Bradford RD; Van Frank BK; Takahashi S; **Adderson EE**
AUTHOR(S) E-MAIL: john.bohnsack@hsc.utah.edu
CORPORATE SOURCE: Univ Utah, Dept Pediat, 50 N Med Dr/Salt Lake City//UT/84132 (REPRINT); Univ Utah, Dept Pediat, /Salt Lake City//UT/84132; Joshi Eiyoh Univ, Chiyoda Ku, /Sakado/Saitama 3500288/Japan/; St Jude Childrens Hosp, Dept Infect Dis, /Memphis//TN/38105
PUBLICATION TYPE: JOURNAL
PUBLICATION: INFECTION AND IMMUNITY, 2002, V70, N1 (JAN), P134-139
GENUINE ARTICLE#: 504FX
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0019-9567
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Human isolates of serotype III Streptococcus **agalactiae** (**group B** streptococcus [**GBS**]) can be divided into three separate phylogenetic lineages based on analysis of the restriction digest patterns (RDPs) of chromosomal DNA. Nine DNA sequences that are present in all isolates of the RDP III-3 phylogenetic lineage, but not in the other

lineages, were identified by genomic subtractive hybridization. A complete physical map of a III-3 chromosome was constructed. Six of the nine III-3-specific sequences mapped to a 340-kb Sse8387I fragment which contains or is located close to known **GBS** virulence genes. One of the III-3-specific probes, AW-10, encodes part of GBSi1, a group II intron that is inserted at two sites within the **GBS** genome. The second chromosomal site for GBSi1 was isolated, sequenced, and mapped to a location near the locus responsible for hemolysin production. These findings suggest that the genetic variation that distinguishes the RDP type III-3 strains from other serotype III strains occurs largely within localized areas of the genome containing known or putative virulence genes.

6/3,AB/7 (Item 7 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12700971 References: 15
TITLE: Phylogenetic classification of serotype III **group B** streptococci on the basis of hylB gene analysis and DNA sequences specific to restriction digest pattern type III-3
AUTHOR(S): **Bohnsack JF (REPRINT)**; Takahashi S; Detrick SR; Pelinka LR ; Hammitt LL; Aly AA; Whiting AA; **Adderson EE**
AUTHOR(S) E-MAIL: john.bohnsack@hsc.utah.edu
CORPORATE SOURCE: Univ Utah, Dept Pediat, 50 N Med Dr/Salt Lake City//UT/84132 (REPRINT); Univ Utah, Dept Pediat, /Salt Lake City//UT/84132; St Jude Childrens Res Hosp, Dept Infect Dis, /Memphis//TN/38105; Joshi Eiyoh Univ, Div Microbiol, /Sakado/Saitama/Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF INFECTIOUS DISEASES, 2001, V183, N11 (JUN 1), P 1694-1697
GENUINE ARTICLE#: 430XZ
PUBLISHER: UNIV CHICAGO PRESS, 1427 E 60TH ST, CHICAGO, IL 60637-2954 USA
ISSN: 0022-1899
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Previous work divided serotype III **group B** streptococci (**GBS**) into 3 major phylogenetic lineages (III-1, III-2, and III-3) on the basis of bacterial DNA restriction digest patterns (RDPs). Most neonatal invasive disease was caused by III-3 strains, which implies that III-3 strains are more virulent than III-2 or III-1 strains. In the current studies, all RDP III-3 and III-1 strains expressed hyaluronate lysase activity; however, all III-2 strains lack hyaluronate lysase activity, because the gene that encodes hyaluronate lysase, hylB, is inactivated by IS1548. Subtractive hybridization was used to identify 9 short DNA sequences that are present in all the III-3 strains but not in any of the III-2 or III-1 strains. With 1 exception, these III-3-specific sequences were not detected in nonserotype III **GBS**. These data further validate the RDP-based subclassification of **GBS** and suggest that lineage-specific genes will be identified, which account for the differences in virulence among the lineages.

6/3,AB/8 (Item 8 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12055954 References: 17
TITLE: Bacterial genetics and human immunity to **group B** streptococci
AUTHOR(S): **Adderson EE (REPRINT)**; Takahashi S; **Bohnsack JF**
CORPORATE SOURCE: St Jude Childrens Hosp, Dept Infect Dis, 332 N Lauderdale/Memphis//TN/38105 (REPRINT); St Jude Childrens Hosp, Dept Infect Dis, /Memphis//TN/38105; Univ Utah, Dept Pediat, /Salt Lake City//UT/84132; Univ Utah, Dept Pathol, /Salt Lake City//UT/84132
PUBLICATION TYPE: JOURNAL
PUBLICATION: MOLECULAR GENETICS AND METABOLISM, 2000, V71, N1-2 (SEP-OCT), P451-454
GENUINE ARTICLE#: 360XQ
PUBLISHER: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA
ISSN: 1096-7192
LANGUAGE: English DOCUMENT TYPE: REVIEW

ABSTRACT: Serotype III **group B** Streptococcus **agalactiae** (**GBS**) are the most common cause of neonatal sepsis and meningitis. We have classified type III **GBS** by restriction digest patterns of chromosomal DNA and demonstrated that a subgroup of genetically related strains (RDP type III-3) causes the majority of type III **GBS** neonatal infection. Genetic differences between type III **GBS** strains contribute significantly to differences in virulence and host immune responses. While 100% of less virulent RDP type III-1 and III-2 organisms express C5a-ase, an inhibitor of neutrophil chemotaxis, only 63% of virulent RDP type III-3 isolates have functional C5a-ase, Functional differences in type III **GBS** C5a-ase are attributable to a shared genetic polymorphism, supporting our genetic classification. The mean capsular sialic acid content of virulent RDP type III-3 strains is significantly higher than that of less virulent strains, suggesting that capsular sialylation is also genetically regulated, C5a-ase is not critical for all RDP type III-3 strains to be invasive because the higher capsular sialic acid content of III-3 strains limits complement activation. The identification of these and additional genetic differences between **GBS** strains has important implications for our understanding of the pathogenesis of these important human infections. (C) 2000 Academic Press.

6/3,AB/9 (Item 9 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11919389 References: 22
TITLE: Genetic polymorphisms of **group B** streptococcus scpB alter functional activity of a cell-associated peptidase that inactivates C5a
AUTHOR(S): **Bohnsack JF**; Takahashi S; Hammitt L; Miller DV; Aly AA; **Adderson EE (REPRINT)**
AUTHOR(S) E-MAIL: Elisabeth.Adderson@STJUDE.org
CORPORATE SOURCE: St Jude Childrens Res Hosp, Dept Infect Dis, 332 N Lauderdale St/Memphis//TN/38105 (REPRINT); St Jude Childrens Res Hosp, Dept Infect Dis, /Memphis//TN/38105; Univ Utah, Dept Pediat, /Salt Lake City//UT/84132; Univ Utah, Dept Pathol, /Salt Lake City//UT/84132; Joshi

Eiyoh Univ, Dept Microbiol, /Sakado/Saitama 3500288/Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: INFECTION AND IMMUNITY, 2000, V68, N9 (SEP), P5018-5025
GENUINE ARTICLE#: 346KM
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0019-9567
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Many **group B** Streptococcus **agalactiae** strains and other pathogenic streptococci express a cell-associated peptidase that inactivates C5a (C5a-ase), the major neutrophil chemoattractant produced by activation of the complement cascade. Type III **group B** streptococci (**GBS**) can be classified genotypically into three restriction digest pattern types. Functional C5a-ase activity of **GBS** correlates with this genetic typing; therefore, me sought to identify a genetic basis for this phenomenon. Southern hybridization confirms that all type III **GBS** contain scpB, the gene encoding **GBS** C5a-ase, **GBS** strains with high C5a-ase functional activity and those with no or very low activity both express immunoreactive C5a-ase. The scpB sequence of strain 130, which has high C5a-ase activity, is 98.2% homologous to the previously reported serotype II **GBS** scpB sequence. The scpB sequences of strains I25 and GW, which have low or no C5a-ase activity, are identical. The predicted I25 and GW C5a-ase proteins share a four-amino-acid deletion affecting the protease histidine active-site consensus motif. Recombinant I30 C5a-ase has good functional activity, whereas recombinant I25 C5a-ase has low activity. These data demonstrate that functional C5a-ase differences between type III **GBS** strains are attributable to a genetic polymorphism of scpB. The ubiquitous expression of C5a-ase, irrespective of functional activity, suggests that C5a-ase may have a second, as yet unidentified, function.

6/3,AB/10 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01249184
ISOLATED GENES FROM VIRULENT **GROUP B** $I(STREPTOCOCCUS **AGALACTIAE**)
ISOLIERTE GENE DER VIRULENTEN GRUPPE -I(STREPTOCOCCUS **AGALACTIAE**)
GENES ISOLES ISSUS DU $I(STREPTOCOCCUS **AGALACTIAE**) DU GROUPE B VIRULENT
PATENT ASSIGNEE:
The University of Utah Research Foundation, (297170), Suite 110, 615 Arapeen Drive, Salt Lake City, UT 84108, (US), (Applicant designated States: all)
INVENTOR:
ADDERSON, Elisabeth, Room D 2038, 332 N. Lauderdale, Memphis, TN 38105, (US)
BOHNSACK, John, 50 North Medical Drive, Salt Lake -City, UT 84132, (US
PATENT (CC, No, Kind, Date):
WO 2000078787 001228
APPLICATION (CC, No, Date): EP 2000943019 000621; WO 2000US17082 000621
PRIORITY (CC, No, Date): US 140084 P 990621

DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C07H-021/04
LANGUAGE (Publication,Procedural,Application): English; English; English

6/3,AB/11 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0290219 DBR Accession No.: 2002-12066 PATENT
New streptococcal matrix adhesion (Ema) polypeptides, useful as vaccines, particularly for treating or preventing infections by virulent forms of streptococci - plasmid, cosmid, yeast artificial chromosome, phage or virus vector-mediated recombinant protein gene transfer and expression in host cell for use in vaccine preparation and bacterium infectiontherapy
AUTHOR: **ADDERSON E; BOHNSACK J**
PATENT ASSIGNEE: ST JUDE CHILDREN'S RES HOSPITAL; UNIV UTAH RES FOUND 2002
PATENT NUMBER: WO 200212294 PATENT DATE: 20020214 WPI ACCESSION NO.: 2002-257465 (200230)
PRIORITY APPLIC. NO.: US 634341 APPLIC. DATE: 20000808
NATIONAL APPLIC. NO.: WO 2001US24795 APPLIC. DATE: 20010808
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Isolated streptococcal polypeptides, which comprise the Streptococcus **agalactiae** matrix adhesion (Ema) polypeptides, are new. The polypeptides comprise EmaA, EmaB, EmaC, EmaD or EmaE. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a vaccine or an immunogenic composition comprising one or more of the streptococcal polypeptides EmaA, EmaB, EmaC, EmaD and/or EmaE, and a pharmaceutical adjuvant; (2) a purified antibody or monoclonal antibody to the streptococcal polypeptide EmaA, EmaB, EmaC, EmaD or EmaE; (3) pharmaceutical compositions comprising: (a) one or more of the streptococcal polypeptides EmaA-E, and a pharmaceutical carrier; (b) the antibodies to the streptococcal polypeptides EmaA-E and a pharmaceutical carrier; or (c) a combination of at least two antibodies to the streptococcal proteins and a pharmaceutical carrier, where at least one antibody to EmaA-E is combined with at least one antibody to a protein selected from Spb1 and Spb2, Rib, Lmb, C5a-ase or C protein alpha antigen; (4) an immortal cell line that produces the monoclonal antibody; (5) isolated nucleic acids encoding the streptococcal polypeptide EmaA, EmaB, EmaC, EmaD or EmaE; (6) a vector comprising the nucleic acid and a promoter; (7) a host vector system for the production of the polypeptide comprising the vector in a host cell; (8) a unicellular host transformed with the recombinant DNA of (5); (9) a nucleic acid vaccine comprising the recombinant DNA of (5); (10) methods for detecting the presence of: (a) the streptococcal polypeptide EmaA, EmaB, EmaC, EmaD or EmaE; or (b) a bacterium having a gene encoding the streptococcal polypeptide EmaA, EmaB, EmaC, EmaD or EmaE; (11) Ema homologous polypeptides from additional bacterial species comprising an isolated: (a) S. pneumoniae Ema polypeptide comprising 304 or 297 amino acids fully defined in the specification; (b) S. pyogenes Ema polypeptide comprising 150 amino acids fully defined in the specification; (c) Enterococcus faecalis Ema

polypeptide comprising 284 amino acids fully defined in the specification; or (d) Corynebacterium diphtheriae Ema polypeptide comprising 348 amino acids fully defined in the specification; (12) isolated nucleic acids encoding the streptococcal polypeptides of (11); (13) methods for preventing infection with a bacterium that expresses a streptococcal Ema polypeptide by administering the vaccine or immunogenic composition; (14) methods for treating or preventing infection with a bacterium expressing a streptococcal Ema polypeptide, or for inducing an immune response in a subject who has been exposed to or infected with a streptococcal bacterium, by administering the pharmaceutical composition of (3); and (15) isolated bacterial polypeptides. BIOTECHNOLOGY - Preferred Polypeptide: The EmaA polypeptide comprises the sequence having 245 amino acids fully defined in the specification, or analogs, variants or immunogenic fragments of this. The EmaB polypeptide comprises the sequence having 307 amino acids fully defined in the specification, or its analogs, variants or immunogenic fragments. The EmaC polypeptide comprises the sequence having 305 amino acids fully defined in the specification, or its analogs, variants or immunogenic fragments. The EmaD polypeptide comprises the sequence having 283 amino acids fully defined in the specification, or its analogs, variants or immunogenic fragments. The EmaE polypeptide comprises the sequence having 903 amino acids fully defined in the specification, or its analogs, variants or immunogenic fragments. The streptococcal polypeptides are preferably labeled with a detectable label. The isolated bacterial polypeptides of (15) comprise an isolated bacterial (streptococcal) polypeptide, which is not isolated from Actinomyces, comprising: TLLTCTPYMIN(S/T)HRLLV(R/K)G. The bacterial polypeptide also comprises: TLVTCTPYGINTHRLLVTA. The isolated bacterial or streptococcal polypeptide may also comprise: TLVTCTPYGVNTKRLLVRG. Preferred Nucleic Acid: The isolated nucleic acid comprises: (a) the DNA sequence comprising 737, 924, 918, 852 or 2712 bp (which encodes streptococcal polypeptide EmaA, EmaB, EmaC, EmaD or EmaE, respectively) fully defined in the specification; (b) DNA sequences that hybridize to the (a) under moderate hybridization conditions; (c) DNA sequences capable of encoding the amino acid sequence encoded by the DNA sequences of (a) or (b); or (d) degenerate variants, alleles or hybridizable fragments of the above. The nucleic acid is a recombinant DNA molecule. Preferably, the DNA molecule is operatively linked to an expression control sequence. The vector has a promoter, which comprises a bacterial, yeast, insect or mammalian promoter. The vector is a plasmid, cosmid, yeast artificial chromosome (YAC), bacteriophage or eukaryotic viral DNA. The isolated nucleic acids encoding the Ema homologous polypeptides of (11) comprise: (a) the DNA sequence comprising 915 or 894 bp, 855 or 1047 bp (which encodes the S. pneumoniae, E. faecalis or C. diphtheriae Ema polypeptide, respectively) fully defined in the specification; (b) DNA sequences that hybridize to the (a) under moderate hybridization conditions; (c) DNA sequences capable of encoding the amino acid sequence encoded by the DNA sequences of (a) or (b); or (d) degenerate variants, alleles or hybridizable fragments of the above. Preferred Composition: The vaccine or immunogenic composition further comprises an antigen selected from the following: (a) the polypeptide Spb1 or its immunogenic fragment; (b) the polypeptide Spb2 or its immunogenic fragment; (c) the polypeptide C protein alpha antigen or its immunogenic fragment; (d) the polypeptide Rib or its immunogenic fragment; (e) the polypeptide Lmb or its immunogenic fragment; (f) the

polypeptide C5a-ase or its immunogenic fragment; (g) **Group B** streptococcal polysaccharides or oligosaccharides; or (h) any combination of one or more of the above. The pharmaceutical composition of (3a) further comprises an active ingredient consisting of: (a) Spb1 or Spb2 polypeptide; (b) C protein alpha antigen; (c) Rib polypeptide; (d) Lmb polypeptide; (e) C5a-ase polypeptide; (f) a **Group B** streptococcal polysaccharide or oligosaccharide; or (g) an anti-streptococcal vaccine. Preferred Antibody: The antibody is preferably labeled with a detectable label. In particular, the label consists of an enzyme, a chemical that fluoresces or a radioactive element. Preferred Host Cell: The host cell comprises a prokaryotic or eukaryotic cell. Preferred Method: In detecting the presence of the streptococcal polypeptide EmaA, EmaB, EmaC, EmaD or EmaE in method (10), the streptococcal polypeptide is measured by: (a) contacting a sample in which the presence or activity of the streptococcal polypeptide EmaA, EmaB, EmaC, EmaD or EmaE is suspected with an antibody to the streptococcal polypeptide under conditions that allow binding of the streptococcal polypeptide to the antibody to occur; and (b) detecting whether binding has occurred between the streptococcal polypeptide in the sample and the antibody. Detection of binding indicates the presence or activity of the streptococcal polypeptide in the sample. Also in method (10), detecting a bacterium having a gene encoding the streptococcal polypeptide EmaA, EmaB, EmaC, EmaD or EmaE comprises: (a) contacting a sample in which the presence or activity of the bacterium is suspected with an oligonucleotide that hybridizes to a streptococcal polypeptide gene selected from emaA, emaB, emaC, emaD or emaE under conditions that allow specific hybridization of the oligonucleotide to the gene to occur; and (b) detecting whether hybridization has occurred between the oligonucleotide and the gene. The detection of hybridization indicates the presence or activity of the bacterium in the sample. ACTIVITY - Antibacterial. No biological data given. MECHANISM OF ACTION - Vaccine. No biological data given. USE - The streptococcal polypeptides are useful as vaccines, particularly for treating or preventing infections by virulent forms of streptococci. ADMINISTRATION - Administration may be parenteral (e.g. transmucosal, transdermal, intramuscular, intravenous or intradermal), oral or nasal. Dosage is 2.5-50 micrograms of total protein per dose. EXAMPLE - No relevant examples given.(177 pages)

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13sep04 10:27:32 User219783 Session D2045.3

Devi, S.
10/009254

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER, PASCAL, DISSABS, FEDRIP' ENTERED AT 11:21:20 ON 13 SEP 2004)

L1 231 S "ADDERSON E"?/AU — Author (s)
L2 449 S "BOHNSACK J"?/AU
L3 79 S L1 AND L2
L4 72 S (L1 OR L2 OR L3) AND AGALACTIAE

L6 72 S L4 AND (GBS OR GROUP B)
L7 32 DUP REM L6 (40 DUPLICATES REMOVED)

L7 ANSWER 1 OF 32 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004332741 EMBASE
TITLE: Serotype III Streptococcus **agalactiae** from bovine milk and human neonatal infections.
AUTHOR: **Bohnsack J.F.**; Whiting A.A.; Martinez G.; Jones N.; **Adderson E.E.**; Detrick S.; Blaschke-Bonkowsky A.J.; Bisharat N.; Gottschalk M.
CORPORATE SOURCE: J.F. Bohnsack, Department of Pediatrics, Univ. of Utah Health Sciences Center, 50 North Medical Drive, Salt Lake City, UT 84132, United States. john.bohnsack@hsc.utah.edu
SOURCE: Emerging Infectious Diseases, (2004) 10/8 (1412-1419). Refs: 22
ISSN: 1080-6040 CODEN: EIDIFA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
007 Pediatrics and Pediatric Surgery
017 Public Health, Social Medicine and Epidemiology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Streptococcus **agalactiae** (**group B** streptococcus [**GBS**]) causes invasive human infections and bovine mastitis. This study examined the genetic relationship between bovine and human serotype III **GBS** by using molecular techniques that classify human serotype III **GBS** into four distinct phylogenetic lineages. Bovine serotype III **GBS** were largely contained in two lineages, which are distinct from the two major lineages (restriction digest types III-2 and III-3) that infect human neonates. One of the bovine lineages closely resembles the human III-1 lineage, whose members occasionally cause human neonatal infections. The bovine strains in the other lineage characteristically have an initiation factor IF2 gene (infB) H allele and multilocus sequence types that are not found in human **GBS** strains. Evidence suggests that this "H allele" lineage is related to the human III-3 lineage. These results support the assertion that human and bovine **GBS** are largely unrelated and provide further insight into the genetic relation between human and bovine **GBS**.

L7 ANSWER 2 OF 32 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004300806 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15150329
TITLE: Equivalence of high-virulence clonotypes of serotype III **group B** Streptococcus **agalactiae**

Searcher : Shears 571-272-2528

(**GBS**).
AUTHOR: Fleming Katherine E; **Bohnsack John F**; Palacios Geraldo C; Takahashi Shinji; **Adderson Elisabeth E**
CORPORATE SOURCE: Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, USA.
CONTRACT NUMBER: P30 CA21765 (NCI)
R01 AI40918 (NIAID)
SOURCE: Journal of medical microbiology, (2004 Jun) 53 (Pt 6) 505-8.
Journal code: 0224131. ISSN: 0022-2615.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AY228464; GENBANK-AY228465; GENBANK-AY228466; GENBANK-AY228467
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 20040624
Last Updated on STN: 20040709
Entered Medline: 20040708

AB Analysis of growth characteristics, multilocus enzyme electrophoresis, restriction digest pattern (RDP) typing and multilocus sequence typing have identified clonotypes of serotype III **group B** Streptococcus **agalactiae** (**GBS**) associated with invasive infection in neonates. This study sought to unify phenotypic and genotypic classifications of type III **GBS** strains associated with increased virulence in newborns. High-virulence clonotype (HVC) strains possessed the translation initiation factor 2 (infB) C allele, found in RDP type III-3 strains, and hybridized with the RDP type III-3-specific probe AA3.6, whereas non-HVC strains shared the infB A allele and genomic DNA from these strains did not hybridize with the AA3.6 probe. The characteristic growth lag of HVC **GBS** at 40 degrees C has been attributed to the presence of a heat-labile fructose-1,6-bisphosphate aldolase (Fba) enzyme in these strains. The deduced amino acid sequence of fba genes of both HVC and non-HVC strains, however, were identical. HVC and RDP type III-3 represent the same genetically related group of bacteria. The characteristic growth differences of virulent strains of type III **GBS**, however, are not directly attributable to differences in fba.

L7 ANSWER 3 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:955440 CAPLUS
DOCUMENT NUMBER: 140:160238
TITLE: Subtractive hybridization identifies a novel predicted protein mediating epithelial cell invasion by virulent serotype III **group B** Streptococcus **agalactiae**
AUTHOR(S): **Adderson, Elisabeth E.**; Takahashi, Shinji; Wang, Yan; Armstrong, Jianling; Miller, Dylan V.; **Bohnsack, John F.**
CORPORATE SOURCE: Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Infection and Immunity (2003), 71(12), 6857-6863
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Group B** S. **agalactiae** bacteria (**group B** streptococci [**GBS**]) are the most common cause of serious bacterial infection in newborn infants. The majority of serotype III-related cases of neonatal disease are caused by a genetically related subgroup of bacteria, restriction fragment digest pattern (RDP) type III-3, suggesting that these strains possess unique genes contributing to virulence. We used genomic subtractive hybridization to identify regions of genomic DNA unique to virulent RDP type III-3 **GBS** strains. Within 1 of these III-3-specific regions is a 1,506-bp open reading frame, spb1 (surface protein of **group B** streptococcus 1). A mutant type III **GBS** strain lacking Spb1 was constructed in virulent RDP type III-3 strain 874391, and the interactions of the wild-type and spb1 isogenic mutant with a variety of epithelial cells important to **GBS** colonization and infection were compared. While adherence of the spb1 isogenic mutant to A549 respiratory, C2Bbe1 colonic, and HeLa cervical epithelial cells was slightly lower than that of the 874391 strain, invasion of the Spb1- mutant was significantly reduced with these cell lines compared to what was seen with 874391. The defect in epithelial invasion was corrected by supplying spb1 in trans. These observations suggest that Spb1 contributes to the pathogenesis of neonatal **GBS** infection by mediating internalization of virulent serotype III **GBS** and confirm that understanding of the population structure of bacteria may lead to insights into the pathogenesis of human infections.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 32 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2003294851 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12791877
TITLE: Multilocus sequence typing system for **group B** streptococcus.
AUTHOR: Jones Nicola; **Bohnsack John F**; Takahashi Shinji; Oliver Karen A; Chan Man-Suen; Kunst Frank; Glaser Philippe; Rusniok Christophe; Crook Derrick W M; Harding Rosalind M; Bisharat Naiel; Spratt Brian G
CORPORATE SOURCE: Nuffield Department of Clinical Laboratory Sciences, Institute for Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom..
nicola.jones@ndcls.ox.ac.uk
SOURCE: Journal of clinical microbiology, (2003 Jun) 41 (6) 2530-6. Journal code: 7505564. ISSN: 0095-1137.
PUB. COUNTRY: United States
DOCUMENT TYPE: (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030626
Last Updated on STN: 20031002
Entered Medline: 20031001

AB A multilocus sequence typing (MLST) system was developed for **group B** streptococcus (**GBS**). The system was used to characterize a collection (n = 152) of globally and ecologically diverse human strains of **GBS** that included representatives of capsular

serotypes Ia, Ib, II, III, V, VI, and VIII. Fragments (459 to 519 bp) of seven housekeeping genes were amplified by PCR for each strain and sequenced. The combination of alleles at the seven loci provided an allelic profile or sequence type (ST) for each strain. A subset of the strains were characterized by restriction digest patterning, and these results were highly congruent with those obtained with MLST. There were 29 STs, but 66% of isolates were assigned to four major STs. ST-1 and ST-19 were significantly associated with asymptomatic carriage, whereas ST-23 included both carried and invasive strains. All 44 isolates of ST-17 were serotype III clones, and this ST appeared to define a homogeneous clone that was strongly associated with neonatal invasive infections. The finding that isolates with different capsular serotypes had the same ST suggests that recombination occurs at the capsular locus. A web site for **GBS** MLST was set up and can be accessed at http://sagalactiae.mlst.net. The **GBS** MLST system offers investigators a valuable typing tool that will promote further investigation of the population biology of this organism.

L7 ANSWER 5 OF 32 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003450636 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14513426
TITLE: Beta-hemolysin-independent induction of apoptosis of macrophages infected with serotype III **group B** streptococcus.
AUTHOR: Ulett Glen C; **Bohnsack John F**; Armstrong Jianling; **Adderson Elisabeth E**
CORPORATE SOURCE: Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.
CONTRACT NUMBER: R01 A140918
SOURCE: Journal of infectious diseases, (2003 Oct 1) 188 (7) 1049-53.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030928
Last Updated on STN: 20031105
Entered Medline: 20031104

AB **Group B** streptococcus (**GBS**) induces apoptosis in macrophages. Growth conditions minimizing beta-hemolysin expression, such as high glucose, reduce apoptosis. We constructed an isogenic mutant strain of **GBS** 874391 lacking the beta-hemolysin structural gene cylE and investigated the role that beta-hemolysin plays in apoptosis of J774 macrophages. Viability of macrophages infected with wild-type or cylE **GBS** was similar and significantly less than that of macrophages infected with **GBS** grown in high-glucose media. Thus, apoptosis in **GBS**-infected macrophages is dependent not on beta-hemolysin but on a factor coregulated with beta-hemolysin by glucose.

L7 ANSWER 6 OF 32 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:260758 BIOSIS
DOCUMENT NUMBER: PREV200300260758

TITLE: Fibronectin-binding proteins of **group B** Streptococcus **agalactiae** (**GBS**).
AUTHOR(S): **Adderson, Elisabeth E.** [Reprint Author]; Wang, Yan; Armstrong, Jianling; **Bohnsack, John F.**
CORPORATE SOURCE: Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, USA
SOURCE: Pediatric Research, (April 2003) Vol. 53, No. 4 Part 2, pp. 315A. print.
Meeting Info.: Annual Meeting of the Pediatric Academic Societies. Seattle, WA, USA. May 03-06, 2003. Pediatric Academic Societies.
ISSN: 0031-3998 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jun 2003
Last Updated on STN: 4 Jun 2003

L7 ANSWER 7 OF 32 EMBASE
on STN
ACCESSION NUMBER: 2003050406 EMBASE
TITLE: A novel streptococcal surface protease promotes virulence, resistance to opsonophagocytosis, and cleavage of human fibrinogen.
AUTHOR: Harris T.O.; Shelver D.W.; **Bohnsack J.F.**; Rubens C.E.
CORPORATE SOURCE: C.E. Rubens, 4800 Sand Point Way NE, Seattle, WA 98105, United States. cruben@chmc.org
SOURCE: Journal of Clinical Investigation, (2003) 111/1 (61-70).
Refs: 54
ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Group B** streptococcus (**GBS**) is an important human pathogen. In this study, we sought to identify mechanisms that may protect **GBS** from host defenses in addition to its capsular polysaccharide. A gene encoding a cell-surface-associated protein (cspA) was characterized from a highly virulent type III **GBS** isolate, COH1. Its sequence indicated that it is a subtilisin-like extracellular serine protease homologous to streptococcal C5a peptidases and caseinases of lactic acid bacteria. The wild-type strain cleaved the α chain of human fibrinogen, whereas a cspA mutant, TOH121, was unable to cleave fibrinogen. We observed aggregated material when COH1 was incubated with fibrinogen but not when the mutant strain was treated similarly. This suggested that the product(s) of fibrinogen cleavage have strong adhesive properties and may be similar to fibrin. The cspA gene was present among representative clinical isolates from all nine capsular serotypes, as revealed by Southern blotting. A cspA(-) mutant was ten times less virulent in a neonatal rat sepsis model of **GBS** infections, as measured by LD(50) analysis. In addition, the cspA(-) mutant was significantly more sensitive than the wild-type strain to opsonophagocytic killing by human neutrophils in vitro. Taken together, the results suggest that cleavage of fibrinogen by CspA may increase the lethality of

GBS infection, potentially by protecting the bacterium from opsonophagocytic killing.

L7 ANSWER 8 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2002:123056 CAPLUS
DOCUMENT NUMBER: 136:162383
TITLE: **Group B** Streptococcus extracellular matrix adhesion polypeptides and nucleic acids and their therapeutic compositions and vaccines
INVENTOR(S): **Adderson, Elisabeth; Bohnsack, John**
PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, USA; University of Utah Research Foundation
SOURCE: PCT Int. Appl., 177 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002012294	A2	20020214	WO 2001-US24795	20010808
WO 2002012294	A3	20030410		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001081168	A5	20020218	AU 2001-81168	20010808
EP 1320542	A2	20030625	EP 2001-959633	20010808
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004071729	A1	20040415	US 2003-333002	20030708
PRIORITY APPLN. INFO.:			US 2000-634341	A1 20000808
			WO 2001-US24795	W 20010808

AB This invention provides isolated nucleic acids encoding polypeptides comprising amino acid sequences of streptococcal matrix adhesion (Ema) polypeptides. The invention provides nucleic acids encoding Streptococcus **agalactiae** Ema polypeptides EmaA, EmaB, EmaC, EmaD and EmaE. The present invention provides isolated polypeptides comprising amino acid sequences of **Group B** streptococcal polypeptides EmaA, EmaB, EmaC, EmaD and EmaE, including analogs, variants, mutants, derivs. and fragments thereof. Ema homologous polypeptides from addnl. bacterial species, including S. pneumoniae, S. pyogenes, Enterococcus faecalis and Corynebacterium diphtheriae are also provided. Antibodies to the Ema polypeptides and immunogenic fragments thereof are also provided. The present invention relates to the identification and prevention of infections by virulent forms of streptococci. This invention provides pharmaceutical compns., immunogenic compns., vaccines, and diagnostic and therapeutic methods of use of the isolated polypeptides, antibodies thereto, and nucleic acids. Assays for compds. which modulate the polypeptides of the present invention for use in therapy are also

provided.

L7 ANSWER 9 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2002:825436 CAPLUS
DOCUMENT NUMBER: 138:148468
TITLE: Correlation of phylogenetic lineages of **group B** Streptococci, identified by analysis of restriction-digestion patterns of genomic DNA, with infB alleles and mobile genetic elements
AUTHOR(S): Takahashi, Shinji; Detrick, Shauna; Whiting, April A.; Blaschke-Bonkowksy, Anne J.; Aoyagi, Youko; **Adderson, Elisabeth E.; Bohnsack, John F.**
CORPORATE SOURCE: Division of Microbiology, Joshi-Eiyoh University, Chiyoda, Sakado, Saitama, Japan
SOURCE: Journal of Infectious Diseases (2002), 186(7), 1034-1038
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phylogenetic lineages of pathogenic Streptococcus **agalactiae** (**group B** streptococci [**GBS**]) can be identified by anal. of restriction-digestion patterns (RDPs) of chromosomal DNA. The purpose of the present study was to correlate **GBS** RDP types and (1) alleles of the highly conserved gene encoding translation-initiation factor IF2, infB, and/or (2) the inserted elements IS1548 and GBSi1. Only 1 combination of serotype and infB allele was found within each RDP type. Strains within a particular RDP type also tend to have the same inserted elements in each of 3 loci examined A novel insertion sequence, designated "IS1563," was found within all RDP type II-2 strains. Most RDP types could be identified by a combination of serotype, infB allele, and inserted elements at each of the loci. These mol. markers can be used to identify **GBS** populations and to correlate RDP types and phylogenetic lineages identified by different methods.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2001:936240 CAPLUS
DOCUMENT NUMBER: 136:196841
TITLE: Long-range mapping of the Streptococcus **agalactiae** phylogenetic lineage restriction digest pattern type III-3 reveals clustering of virulence genes
AUTHOR(S): **Bohnsack, John F.**; Whiting, April A.; Bradford, Russell D.; Van Frank, Brenna K.; Takahashi, Shinji; **Adderson, Elisabeth E.**
CORPORATE SOURCE: Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City, UT, 84132, USA
SOURCE: Infection and Immunity (2002), 70(1), 134-139
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human isolates of serotype III S. **agalactiae** (**group**

B streptococcus [**GBS**]) can be divided into 3 sep. phylogenetic lineages based on anal. of the restriction digest patterns (RDPs) of chromosomal DNA. Nine DNA sequences that are present in all isolates of the RDP III-3 phylogenetic lineage, but not in the other lineages, were identified by genomic subtractive hybridization. A complete phys. map of a III-3 chromosome was constructed. Six of the 9 III-3-specific sequences mapped to a 340-kb Sse8387I fragment which contains or is located close to known **GBS** virulence genes. One of the III-3-specific probes, AW-10, encodes part of GBSi1, a group II intron that is inserted at 2 sites within the **GBS** genome. The 2nd chromosomal site for GBSi1 was isolated, sequenced, and mapped to a location near the locus responsible for hemolysin production These findings suggest that the genetic variation that distinguishes the RDP type III-3 strains from other serotype III strains occurs largely within localized areas of the genome containing known or putative virulence genes.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 32 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:584955 BIOSIS
DOCUMENT NUMBER: PREV200200584955
TITLE: The role of **group B** streptococcal hemolysin in host cell death.
AUTHOR(S): Ulett, G. C. [Reprint author]; **Bohnsack, J. F.**; Armstrong, J. L. [Reprint author]; **Adderson, E. E.** [Reprint author]
CORPORATE SOURCE: St. Jude Children's Research Hospital, Memphis, TN, USA
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2002) Vol. 102, pp. 82. print. Meeting Info.: 102nd General Meeting of the American Society for Microbiology. Salt Lake City, UT, USA. May 19-23, 2002. American Society for Microbiology. ISSN: 1060-2011.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Nov 2002
Last Updated on STN: 13 Nov 2002

AB Background: Alveolar macrophages are an important early defense mechanism against respiratory pathogens. Streptococcus **agalactiae** (**GBS**) has recently been shown to survive inside macrophages for prolonged periods following nonopsonic phagocytosis and to induce macrophage apoptosis. Conditions used to block expression of and inhibit activity of b-hemolysin reduced macrophage apoptosis, suggesting a role for this virulence factor in host cell death (J Immunol 2000 165:3923). To clarify the role of b-hemolysin in macrophage invasion, intracellular survival and apoptosis, we compared an isogenic b-hemolysin deficient mutant of serotype III strain 874391 to the WT strain. Methods: The b-hemolysin deficient isogenic mutant was created by insertional deletion of the cylE gene by homologous recombination. J774 macrophages were infected at a ratio of 100 bacteria per Mf for 2 h, followed by killing of extracellular bacteria with penicillin and gentamicin. Intracellular survival of **GBS** was assessed by colony counts, and macrophage survival was determined by trypan blue exclusion. Detection of DNA fragmentation and TUNEL staining was used to assess apoptosis. Results:

Following the infection period, similar numbers of the b-hemolysin deficient mutant were recovered from macrophages when compared to the WT strain (5X106 CFU per 5X105 Mf). Viable intracellular **GBS** were detected for 72 h, and there was no significant difference in the survival kinetics of the b-hemolysin deficient mutant when compared to the WT strain. Apoptosis of macrophages was first detected at 48 h in macrophages infected with both the b-hemolysin deficient mutant or the WT strain. By 96 h, 75% of macrophages infected with both the b-hemolysin deficient mutant or the WT strain were non-viable. Conclusions: Apoptosis induced by **GBS** may contribute to a defective inflammatory response during **GBS** infection by manipulating macrophage cell death pathways. In serotype III **GBS**, b-hemolysin does not affect nonopsonic phagocytosis by macrophages or intracellular survival of bacteria, and does not appear to contribute to the induction of apoptosis in macrophages.

L7 ANSWER 12 OF 32 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001187087 EMBASE

TITLE: Phylogenetic classification of serotype III **group B** streptococci on the basis of hylB gene analysis and DNA sequences specific to restriction digest pattern type III-3.

AUTHOR: **Bohnsack J.F.**; Takahashi S.; Detrick S.R.; Pelinka L.R.; Hammitt L.L.; Aly A.A.; Whiting A.A.; **Adderson E.E.**

CORPORATE SOURCE: Dr. J.F. Bohnsack, Dept. of Pediatrics, Univ. of Utah Health Sciences Center, 50 North Medical Dr., Salt Lake City, UT 84132, United States. john.bohnsack@hsc.utah.edu

SOURCE: Journal of Infectious Diseases, (1 Jun 2001) 183/11 (1694-1697).
Refs: 15
ISSN: 0022-1899 CODEN: JIDIAQ

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Previous work divided serotype III **group B** streptococci (**GBS**) into 3 major phylogenetic lineages (III-1, III-2, and III-3) on the basis of bacterial DNA restriction digest patterns (RDPs). Most neonatal invasive disease was caused by III-3 strains, which implies that III-3 strains are more virulent than III-2 or III-1 strains. In the current studies, all RDP III-3 and III-1 strains expressed hyaluronate lysase activity; however, all III-2 strains lack hyaluronate lysase activity, because the gene that encodes hyaluronate lysase, hylB, is inactivated by IS1548. Subtractive hybridization was used to identify 9 short DNA sequences that are present in all the III-3 strains but not in any of the III-2 or III-1 strains. With 1 exception, these III-3-specific sequences were not detected in nonserotype III **GBS**. These data further validate the RDP-based subclassification of **GBS** and suggest that lineage-specific genes will be identified, which account for the differences in virulence among the lineages.

L7 ANSWER 13 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:911278 CAPLUS
DOCUMENT NUMBER: 134:70361
TITLE: Isolated spb1 and spb2 genes from virulent **Group B** Streptococcus **agalactiae** and their uses as vaccines and for diagnosis
INVENTOR(S): **Adderson, Elisabeth; Bohnsack, John**
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078787	A1	20001228	WO 2000-US17082	20000621
WO 2000078787	C2	20020627		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-140084P P 19990621
AB The present invention relates to the identification and prevention of infections by virulent forms of **Group B** streptococci. Disclosed herein is the identification of two genes, spb1 and spb2, that are specific to virulent type III-3 **GBS**. Also disclosed herein are diagnostic methods for detecting virulent **GBS** infections and methods of immunizing a mammal against these bacteria.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2000:603704 CAPLUS
DOCUMENT NUMBER: 134:96041
TITLE: Genetic polymorphisms of **group B** streptococcus scpB alter functional activity of a cell-associated peptidase that inactivates C5a
AUTHOR(S): **Bohnsack, John F.**; Takahashi, Shinji; Hammitt, Laura; Miller, Dylan V.; Aly, Adrienne A.; **Adderson, Elisabeth E.**
CORPORATE SOURCE: Departments of Pediatrics and Pathology, University of Utah School of Medicine, Salt Lake City, UT, 84132, USA
SOURCE: Infection and Immunity (2000), 68(9), 5018-5025
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Many **group B** Streptococcus **agalactiae** strains and other pathogenic streptococci express a cell-associated peptidase that inactivates C5a (C5a-ase), the major neutrophil chemoattractant produced by activation of the complement cascade. Type III **group B** streptococci (**GBS**) can be classified genotypically into three restriction digest pattern types. Functional C5a-ase activity of **GBS** correlates with this genetic typing; therefore, we sought to identify a genetic basis for this phenomenon. Southern hybridization confirms that all type III **GBS** contain scpB, the gene encoding **GBS** C5a-ase. **GBS** strains with high C5a-ase functional activity and those with no or very low activity both express immunoreactive C5a-ase. The scpB sequence of strain I30, which has high C5a-ase activity, is 98.2% homologous to the previously reported serotype II **GBS** scpB sequence. The scpB sequences of strains I25 and GW, which have low or no C5a-ase activity, are identical. The predicted I25 and GW C5a-ase proteins share a four-amino-acid deletion affecting the protease histidine active-site consensus motif. Recombinant I30 C5a-ase has good functional activity, whereas recombinant I25 C5a-ase has low activity. These data demonstrate that functional C5a-ase differences between type III **GBS** strains are attributable to a genetic polymorphism of scpB. The ubiquitous expression of C5a-ase, irresp. of functional activity, suggests that C5a-ase may have a second, as yet unidentified, function.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 32 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 2000269137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10811000
TITLE: Induction of cyclooxygenase-2 by human monocytes exposed to **group B** streptococci.
AUTHOR: Maloney C G; Thompson S D; Hill H R; **Bohnsack J F**; McIntyre T M; Zimmerman G A
CORPORATE SOURCE: Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City 84132, USA.. chris.maloney@hci.utah.edu
CONTRACT NUMBER: AI-13150 (NIAID)
P50 HL-50153 (NHLBI)
SOURCE: Journal of leukocyte biology, (2000 May) 67 (5) 615-21. Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000613
Last Updated on STN: 20000613
Entered Medline: 20000601

AB **Group B** streptococcal (**GBS**) infections are associated with high morbidity and mortality. The molecular pathways mediating the pathophysiological events in **GBS** infection are not fully delineated. Cyclooxygenases (COX) are the enzymes that convert arachidonate to active eicosanoids. To identify the effects of **GBS** on eicosanoid metabolism and regulatory mechanisms, we exposed human monocytes to **GBS** and found that they secreted

prostaglandin E2, prostacyclin, and thromboxane A2. Exposure to **GBS** caused monocytes to express COX-2 mRNA and protein in both a time- and concentration-dependent manner that correlated with eicosanoid production. COX-1 protein was unchanged. Addition of the anti-inflammatory cytokines interleukin (IL)-4 or IL-10 markedly attenuated **GBS**-induced COX-2 protein accumulation after **GBS** exposure, as did inhibition of p38 MAPK. Our experiments are the first to show that exposure of monocytes to a gram-positive bacterium (**GBS**) results in induction of functional COX-2, suggesting that eicosanoids may play important roles in the pathogenesis of **GBS** infections.

L7 ANSWER 16 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 2000:668026 CAPLUS
DOCUMENT NUMBER: 133:348748
TITLE: Bacterial Genetics and Human Immunity to **Group B** Streptococci
AUTHOR(S): **Adderson, Elisabeth E.**; Takahashi, Shinji; **Bohnsack, John F.**
CORPORATE SOURCE: Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Molecular Genetics and Metabolism (2000), 71(1/2), 451-454
CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 17 refs. Serotype III **group B** Streptococcus **agalactiae** (**GBS**) are the most common cause of neonatal sepsis and meningitis. We have classified type III **GBS** by restriction digest patterns of chromosomal DNA and demonstrated that a subgroup of genetically related strains (RDP type III-3) causes the majority of type III **GBS** neonatal infection. Genetic differences between type III **GBS** strains contribute significantly to differences in virulence and host immune responses. While 100% of less virulent RDP type III-1 and III-2 organisms express C5a-ase, an inhibitor of neutrophil chemotaxis, only 63% of virulent RDP type III-3 isolates have functional C5a-ase. Functional differences in type III **GBS** C5a-ase are attributable to a shared genetic polymorphism, supporting our genetic classification. The mean capsular sialic acid content of virulent RDP type III-3 strains is significantly higher than that of less virulent strains, suggesting that capsular sialylation is also genetically regulated. C5a-ase is not critical for all RDP type III-3 strains to be invasive because the higher capsular sialic acid content of III-3 strains limits complement activation. The identification of these and addnl. genetic differences between **GBS** strains has important implications for our understanding of the pathogenesis of these important human infections. (c) 2000 Academic Press.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 32 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:528731 BIOSIS
DOCUMENT NUMBER: PREV200100528731

TITLE: Type I **GBS** directly activate human complement to produce more C5A than do type III **GBS**.
AUTHOR(S): Woods, J. S. [Reprint author]; **Adderson, E. E.** [Reprint author]; **Bohnsack, J. F.** [Reprint author]
CORPORATE SOURCE: Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City, UT, 84132, USA
SOURCE: Journal of Investigative Medicine, (January, 2000) Vol. 48, No. 1, pp. 44A. print.
Meeting Info.: Meeting of the American Federation for Medical Research, Western Region. Carmel, California, USA. February 09-12, 2000.
ISSN: 1081-5589.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Nov 2001
Last Updated on STN: 23 Feb 2002

L7 ANSWER 18 OF 32 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 1999185013 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10085029
TITLE: Capsular sialic acid limits C5a production on type III **group B** streptococci.
AUTHOR: Takahashi S; Aoyagi Y; **Adderson E E**; Okuwaki Y; **Bohnsack J F**
CORPORATE SOURCE: Department of Microbiology, Joshi-Eiyoh University, Sakado, Saitama, 350-0088, Japan.
CONTRACT NUMBER: AI-13150 (NIAID)
AI-40918 (NIAID)
SOURCE: Infection and immunity, (1999 Apr) 67 (4) 1866-70.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 20000303
Entered Medline: 19990426

AB The majority of type III **group B** streptococcus (**GBS**) human neonatal infections are caused by a genetically related subgroup called III-3. We have proposed that a bacterial enzyme, C5a-ase, contributes to the pathogenesis of neonatal infections with **GBS** by rapidly inactivating C5a, a potent pro-inflammatory molecule, but many III-3 strains do not express C5a-ase. The amount of C5a produced in serum following incubation with representative type III strains was quantitated in order to better understand the relationship between C5a production and C5a-ase expression. C5a production following incubation of bacteria with serum depleted of antibody to the bacterial surface was inversely proportional to the sialic acid content of the bacterial capsule, with the more heavily sialylated III-3 strains generating less C5a than the less-virulent, less-sialylated III-2 strains. The amount of C5a produced correlated significantly with C3 deposition on each bacterial strain. Repletion with type-specific antibody caused increased C3b deposition and C5a production through alternative pathway activation, but C5a was

functionally inactivated by strains that expressed C5a-ase. The increased virulence of III-3 strains compared to that of III-2 strains results at least partially from the higher sialic acid content of III-3 strains, which inhibits both opsonophagocytic killing and C5a production in the absence of type-specific antibody. We propose that C5a-ase is not necessary for III-3 strains to cause invasive disease because the high sialic acid content of III-3 strains inhibits C5a production.

L7 ANSWER 19 OF 32 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 1998194619 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9534996
TITLE: Identification of a highly encapsulated, genetically related group of invasive type III **group B** streptococci.
AUTHOR: Takahashi S; **Adderson E E**; Nagano Y; Nagano N; Briesacher M R; **Bohnsack J F**
CORPORATE SOURCE: Department of Microbiology, Joshi-Eiyoh University, Sakado, Japan.
CONTRACT NUMBER: AI-13150 (NIAID)
SOURCE: Journal of infectious diseases, (1998 Apr) 177 (4) 1116-9. Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980430
Last Updated on STN: 19980430
Entered Medline: 19980421

AB Type III **group B** streptococci (**GBS**) isolated from Tokyo and Salt Lake City were classified according to the similarity of HindIII and Sse83871 restriction digest patterns (RDPs) of bacterial DNA. The bacteria were clustered into three RDP types, with excellent correlation between subtyping based on the two enzymes. The majority (91%) of invasive isolates obtained from neonates were RDP type III-3. The mean sialic acid content of the III-3 strains was higher than that of other type III strains. Closely related isolates were concordant for expression of the bacterial enzyme C5a-ase, but invasive strains were no more likely to be C5a-ase positive than were strains isolated from the genitourinary tract of pregnant women. These data indicate that a group of genetically related organisms with increased capsule production causes the majority of invasive type III **GBS** disease.

L7 ANSWER 20 OF 32 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 97240680 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9086140
TITLE: A role for C5 and C5a-ase in the acute neutrophil response to **group B** streptococcal infections.
AUTHOR: **Bohnsack J F**; Widjaja K; Ghazizadeh S; Rubens C E; Hillyard D R; Parker C J; Albertine K H; Hill H R
CORPORATE SOURCE: Department of Pediatrics, University of Utah School of Medicine, Salt Lake City 84132, USA.
CONTRACT NUMBER: AI-13150 (NIAID)
SOURCE: Journal of infectious diseases, (1997 Apr) 175 (4) 847-55. Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970424
Last Updated on STN: 20000303
Entered Medline: 19970417

AB Congenic C5-deficient and C5-sufficient mice were infected with **group B** streptococci (**GBS**) to determine if the polymorphonuclear leukocyte (PMNL) chemoattractant C5a contributes to PMNL recruitment in **GBS** infection and if **GBS** C5a-ase reduces C5a-induced PMNL recruitment in vivo. PMNL accumulation was greater in the peritoneum and air spaces of C5-sufficient mice than in C5-deficient mice. Administration of human C5 to C5-deficient mice caused a significant increase in PMNL recruitment following infection with C5a-ase-negative **GBS**. **GBS** C5a-ase did not reduce PMNL accumulation in C5-sufficient mice but reduced PMNL recruitment in C5-deficient mice reconstituted with human C5. These data indicate that C5a is important for rapid PMNL recruitment to sites of **GBS** infection and that **GBS** C5a-ase inactivates human, but not murine, C5a in vivo. Reduction of the acute inflammatory response by C5a-ase likely contributes to **GBS** virulence in human neonates.

L7 ANSWER 21 OF 32 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 95270302 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7751028
TITLE: Effects of fibronectin and **group B** streptococci on tumour necrosis factor-alpha production by human culture-derived macrophages.
AUTHOR: Peat E B; Augustine N H; Drummond W K; **Bohnsack J F** ; Hill H R
CORPORATE SOURCE: Department of Pathology, University of Utah, School of Medicine, Salt Lake City 84132, USA.
CONTRACT NUMBER: AI-13150 (NIAID)
AI-26733 (NIAID)
SOURCE: Immunology, (1995 Mar) 84 (3) 440-5.
Journal code: 0374672. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950629
Last Updated on STN: 19950629
Entered Medline: 19950619

AB **Group B** streptococci (**GBS**) are an important cause of sepsis and shock in the new-born. We have previously reported that **GBS** induce the production of tumour necrosis factor-alpha (TNF-alpha) by human monocytes and culture-derived macrophages. We have also shown that fibronectin (FN) promotes interaction between **GBS** and human phagocytes. In the present study, we investigated the effect of FN and **GBS** on the production of TNF-alpha by adult and neonatal culture-derived macrophages. We report that soluble FN alone was a strong stimulus for the production of TNF-alpha by culture-derived macrophages (FN 50 micrograms/ml = 623.33 +/- 47 pg/ml TNF, versus media alone 3 +/- 1.5 pg/ml; $P < 0.0001$). While **GBS** also induce the production of

TNF-alpha by macrophages, the addition of FN to **GBS** had more than an additive effect on TNF-alpha levels. FN-mediated TNF-alpha production by macrophages was inhibited by both soluble arginine-glycine-aspartic acid (RGD) peptide (71%; P < 0.0001) and anti-beta 3-integrin monoclonal antibody 7G2 (54%; P < 0.0001). Neonatal culture-derived macrophages produced significantly more TNF-alpha in response to **GBS** (356.4 pg/ml +/- 27.7) than adult cells did (222.0 pg/ml +/- 21.0; P = 0.037), and dramatically more in response to FN alone (neonatal 1931.0 pg/ml +/- 23.0 versus adult 463.5 43.5 pg/ml; P < 0.0001). FN may contribute to the high levels of TNF-alpha production implicated in the pathophysiology of **GBS** sepsis and shock.

L7 ANSWER 22 OF 32 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 93273479 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8388860
TITLE: Mechanism of fibronectin enhancement of **group B** streptococcal phagocytosis by human neutrophils and culture-derived macrophages.
AUTHOR: Hill H R; Augustine N H; Williams P A; Brown E J; **Bohnsack J F**
CORPORATE SOURCE: Department of Pathology and Pediatrics, University of Utah, Salt Lake City 84132.
CONTRACT NUMBER: AI-13150 (NIAID)
AI-24674 (NIAID)
AI-26733 (NIAID)
+
SOURCE: Infection and immunity, (1993 Jun) 61 (6) 2334-9.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930716
Last Updated on STN: 19930716
Entered Medline: 19930628

AB In previous studies, we reported that fibronectin (FN) markedly enhances phagocytic uptake of antibody-coated **group B** streptococci (**GBS**) by human polymorphonuclear leukocytes. Furthermore, administration of FN along with a **GBS** type-specific monoclonal or polyclonal antibody to infected neonatal rats significantly enhances survival. In this study, we have examined the molecular mechanism of this enhancement through phagocyte receptors which recognize the Arg-Gly-Asp (RGD) peptide sequences contained within the FN molecule. Incubation of human polymorphonuclear leukocytes or culture-derived macrophages on coverslips coated with GRGDSP but not GRGESP markedly enhanced uptake of immunoglobulin G-coated **GBS**. The enhancing effect of the RGD-containing peptides was blocked by monoclonal antibodies B6H12 (directed against the integrin-associated protein) and 7G2 (directed against the beta 3-integrin receptor for RGD). These data suggest that FN enhancement of antibody-coated **GBS** uptake is mediated by the critical RGD sequence. Furthermore, this active peptide sequence may have an important role in immunotherapy of bacterial infections, especially in patients with decreased plasma FN concentrations.

L7 ANSWER 23 OF 32 MEDLINE on STN DUPLICATE 16

ACCESSION NUMBER: 93202747 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8454345
TITLE: Restricted ability of **group B** streptococcal C5a-ase to inactivate C5a prepared from different animal species.
AUTHOR: **Bohnsack J F**; Chang J K; Hill H R
CORPORATE SOURCE: Department of Pediatrics, University of Utah School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI-13150 (NIAID)
AI-26733 (NIAID)
SOURCE: Infection and immunity, (1993 Apr) 61 (4) 1421-6.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930507
Last Updated on STN: 20000303
Entered Medline: 19930422

AB Most strains of **group B** streptococci (**GBS**) elaborate a cell surface-associated enzyme that rapidly inactivates the human complement-derived chemoattractants C5a and C5adesarg by cleaving the His-Lys bond at positions 67 and 68 in the C5a molecule. We have suggested that rapid inactivation of C5a and C5adesarg by this enzyme, called C5a-ase, can hinder the inflammatory response at sites of **GBS** infection. We tested the ability of **GBS** C5a-ase to inactivate C5a preparations from various animal species to determine the proper species for studying the role of **GBS** C5a-ase in the pathogenesis of **GBS** infections. Exposure of C5a preparations from humans, monkeys, and cows to **GBS** caused inhibition of C5a functional activity as measured by the ability of C5a to stimulate human polymorphonuclear leukocyte (PMN) adherence and human PMN chemotaxis. Bovine PMN chemotaxis to bovine C5a was also abolished after exposure of bovine C5a to **GBS**. In contrast, mouse, rat, guinea pig, rabbit, pig, and sheep C5a preparations retained full functional activity after exposure to **GBS** as measured by chemotaxis of human PMNs, PMNs from the same animal species, or both. These data suggest that there are structural differences between C5a proteins from different species which alter their susceptibility to **GBS** C5a-ase and indicate that most commonly used animal models of human **GBS** infection are inadequate for detection of a contribution of **GBS** C5a-ase to **GBS** virulence.

L7 ANSWER 24 OF 32 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 93347077 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8345430
TITLE: Production of tumor necrosis factor by human cells in vitro and in vivo, induced by **group B** streptococci.
AUTHOR: Williams P A; **Bohnsack J F**; Augustine N H; Drummond W K; Rubens C E; Hill H R
CORPORATE SOURCE: Department of Pathology, University of Utah School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI 13150 (NIAID)
AI 22498 (NIAID)

AI 26733 (NIAID)
SOURCE: Journal of pediatrics, (1993 Aug) 123 (2) 292-300.
Journal code: 0375410. ISSN: 0022-3476.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19930924
Last Updated on STN: 19930924
Entered Medline: 19930909

AB Tumor necrosis factor alpha (TNF alpha) has been implicated as one of the major mediators of the gram-negative septic shock syndrome. In our studies, **group B** streptococci (**GBS**) induced the production of TNF alpha by human mononuclear cells in a dose- and time-dependent manner. Human mixed mononuclear cell cultures exposed to an encapsulated (657.6 +/- 71.3 pg/ml; n = 30 preparations) or an unencapsulated transposon mutant of type III **GBS** (755.8 +/- 54.7 pg/ml; n = 9) produced similar amounts of TNF alpha. Isolated monocytes and culture-derived macrophages produced higher amounts of TNF alpha (1565 +/- 211 and 1790 +/- 928 pg/ml respectively) in response to **GBS** than did mixed mononuclear cell cultures. In response to **GBS**, mixed mononuclear cells from neonates produced significantly more TNF alpha (729.1 +/- 45 vs 520.3 +/- 47.2 pg/ml; p = 0.004) than did cells from adults. Examination of specimens from patients with neonatal **GBS** disease revealed detectable levels of TNF alpha (7 to 424 pg/ml) in the serum of 5 of 10 patients with sepsis, in 5 of 5 urine samples from infants with sepsis, and in the cerebrospinal fluid of 1 patient with meningitis. These results suggest both a major role for TNF alpha in the pathogenesis of human neonatal **GBS** sepsis and shock and a potential role for immunotherapy directed against this cytokine in this fulminant neonatal bacterial infection.

L7 ANSWER 25 OF 32 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 92176652 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1541826
TITLE: Comparison of the opsonic and complement triggering activity of human monoclonal IgG1 and IgM antibody against **group B** streptococci.
AUTHOR: Shyur S D; Raff H V; **Bohnsack J F**; Kelsey D K; Hill H R
CORPORATE SOURCE: Department of Pathology, University of Utah School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI 13150 (NIAID)
AI 26733 (NIAID)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1992 Mar 15) 148 (6) 1879-84.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
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ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
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Entered Medline: 19920409

Searcher : Shears 571-272-2528

AB We have compared the opsonic and complement-triggering activity of transfectoma-derived, class-switched human IgG1 and IgM mAb (HumAb) against types Ia, II and III **group B** streptococci (**GBS**). These antibodies appear to be directed against the common **group B** cell wall Ag of these organisms. The HumAb IgM promotes uptake of type Ia and II **GBS** at concentrations as low as 37 ng/ml and type III **GBS** at concentrations of 150 ng/ml in the presence of human neonatal complement. In contrast, the IgG1 **GBS** HumAB showed no detectable opsonic activity in concentrations up to 600 ng/ml. When the concentration of HumAb IgG1 is raised to 2.5 micrograms/ml, significant opsonic activity against **GBS** is detected and when the concentration is approximately 40 micrograms/ml, the opsonic activity peaked at a slightly higher level than that with the HumAb IgM. Thus, approximately 100- fold higher concentrations of the IgG1 than the IgM HumAb are required for optimal opsonization. The opsonic activity of the IgM and IgG1 HumAb are closely related to their ability to consume complement and deposit C3 on the surface of type Ia, II, and III **GBS** (r = 0.959). We believe that the marked opsonic and protective activity of the IgM **GBS** HumAb is due to its enhanced avidity and ability to trigger the complement system. Further studies are indicated to determine the feasibility of employing human IgM antibody preparations in the immunotherapy of neonatal **GBS** disease.

L7 ANSWER 26 OF 32 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 92113338 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1730898
TITLE: Bacterial evasion of the antibody response: human IgG antibodies neutralize soluble but not bacteria-associated **group B** streptococcal C5a-ase.
AUTHOR: **Bohnsack J F**; Zhou X N; Gustin J N; Rubens C E; Parker C J; Hill H R
CORPORATE SOURCE: Department of Pediatrics, University of Utah, School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI-13150 (NIAID)
AI-22498 (NIAID)
AI-26733 (NIAID)
+
SOURCE: Journal of infectious diseases, (1992 Feb) 165 (2) 315-21.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920308
Last Updated on STN: 20000303
Entered Medline: 19920220

AB Most strains of **group B** streptococci (**GBS**) possess an enzyme that inactivates the human anaphylatoxin C5a by cleaving a heptapeptide from the carboxyl terminus of C5a. This enzyme, called **GBS** C5a-ase, has been purified to homogeneity and cleaves and inactivates C5a in physiologic buffer. The enzymatic activity of soluble C5a-ase is completely inhibited, however, in the presence of plasma or serum from normal human adults. The neutralization of soluble C5a-ase by plasma and serum results largely from naturally occurring IgG antibodies

directed against C5a-ase. IgG does not neutralize C5a-ase present on intact encapsulated type III **GBS** but does neutralize the C5a-ase activity associated with a transposon-induced mutant strain of type III **GBS** that lacks capsule. The location of **GBS** C5a-ase on the surface of encapsulated type III **GBS** permits the C5a-ase to inactivate C5a while evading neutralization by IgG antibodies.

L7 ANSWER 27 OF 32 MEDLINE on STN
ACCESSION NUMBER: 91144547 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1996961
TITLE: **Group B** streptococci inactivate complement component C5a by enzymic cleavage at the C-terminus.
AUTHOR: **Bohnsack J F**; Mollison K W; Buko A M; Ashworth J C; Hill H R
CORPORATE SOURCE: Department of Pediatrics, University of Utah School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI13150 (NIAID)
SOURCE: Biochemical journal, (1991 Feb 1) 273 (Pt 3) 635-40. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910412
Last Updated on STN: 20000303
Entered Medline: 19910327

AB Incubation of recombinant human C5a (rC5a) with the 7360 strain of **group B** streptococci (**GBS**) destroyed the ability of rC5a to stimulate chemotaxis or adherence of purified human polymorphonuclear leucocytes (PMNs). Treatment of 125I-labelled rC5a with **GBS** 7360 correspondingly decreased rC5a binding to human PMNs. This also resulted in an approx. 600 Da decrease in the molecular mass of rC5a as determined by SDS/PAGE. Incubation of rC5a with the **GBS** strain GW, which only minimally altered the ability of rC5a to activate human PMNs, did not affect rC5a binding to PMNs and did not alter the molecular mass of rC5a on SDS/PAGE. Plasma-desorption m.s. of rC5a inactivated by **GBS** 7360 showed that the **GBS** cleaved the rC5a between histidine-67 and lysine-68 near the C-terminus of rC5a. This mechanism of inactivation of C5a by proteolytic cleavage at the C-terminus of C5a is consistent with the known critical role of the C-terminus in C5a activation of human PMNs. This C5a-cleaving proteinase activity may contribute to the pathophysiology of **GBS** infections.

L7 ANSWER 28 OF 32 MEDLINE on STN
ACCESSION NUMBER: 92002137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1911845
TITLE: Purification of the proteinase from **group B** streptococci that inactivates human C5a.
AUTHOR: **Bohnsack J F**; Zhou X N; Williams P A; Cleary P P; Parker C J; Hill H R
CORPORATE SOURCE: Department of Pediatrics, University of Utah School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI13150 (NIAID)

AI26733 (NIAID)
DK35830 (NIDDK)
SOURCE: Biochimica et biophysica acta, (1991 Aug 30) 1079 (2) 222-8.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 20000303
Entered Medline: 19911030

AB We previously reported that **group B** streptococci (**GBS**) possess a cell-associated activity that inactivates the chemotactic activity generated in zymosan-activated serum by cleaving a specific site within the carboxy termini of C5a and C5adesarg. This inactivates the major chemoattractants for neutrophils that are generated when serum complement is activated. We now report the isolation of the enzyme responsible for the proteolytic cleavage of C5a. Treatment of **GBS** with mutanolysin, an endo-N-acetyl muramidase, released activity from **GBS** which destroyed the functional activity of C5a. The soluble activity was purified to homogeneity by hydroxyapatite, ion-exchange and gel-filtration chromatography. Analysis by SDS-PAGE showed that the enzyme (**GBS** C5a-ase) has an Mr of approx. 120,000. The **GBS** C5a-ase appears to be a serine esterase on the basis of its sensitivity to di-isopropyl fluorophosphate. This enzyme is distinct from the C5a-cleaving enzyme produced by group A streptococci, since the two bacterial products migrate differently on SDS-PAGE, and lack antigenic cross reactivity. This enzyme may play a role in the pathogenesis of **group B** streptococcal disease through its ability to rapidly inactivate the potent neutrophil agonist, C5a, at sites of infection.

L7 ANSWER 29 OF 32 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 90131863 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2405069
TITLE: Effect of fibronectin on IgA-mediated uptake of type III **group B** streptococci by phagocytes.
AUTHOR: Yang K D; **Bohnsack J F**; Hawley M M; Augustine N H; Knape W A; Egan M L; Pritchard D G; Hill H R
CORPORATE SOURCE: Department of Pathology, University of Utah School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI-13150 (NIAID)
AI-19094 (NIAID)
AI-19941 (NIAID)
+
SOURCE: Journal of infectious diseases, (1990 Feb) 161 (2) 236-41.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328

Searcher : Shears 571-272-2528

Entered Medline: 19900309

AB Previous studies have shown that a type-specific IgA monoclonal antibody alone or in combination with fibronectin (Fn) enhances protective efficacy in two animal models of **group B** streptococcal infection. To investigate the mechanisms by which IgA mediates protection, the effects of Fn on phagocytosis of **group B** streptococci (**GBS**) opsonized with a type III-specific IgA monoclonal antibody were examined. Specific IgA alone or in combination with Fn did not promote the phagocytosis of **GBS** by polymorphonuclear leukocytes (PMNL). Fibronectin also had no significant effect on phagocytosis of IgA-opsonized **GBS** by monocytes. Specific IgA alone promoted phagocytosis of **GBS** by culture-derived macrophages in a dose-dependent fashion. Fibronectin enhanced macrophage uptake of the **GBS** opsonized in a suboptimal concentration of specific IgA (phagocytic index = 2.32 +/- 0.56 vs. 3.26 +/- 0.48 with Fn; P less than .05). These data suggest that protection against **GBS** in neonatal rats by a combination of Fn and specific IgA is mediated by macrophages rather than by PMNL or monocytes. Fibronectin may have a critical role in host defense at sites where IgA and macrophages predominate.

L7 ANSWER 30 OF 32 MEDLINE on STN
ACCESSION NUMBER: 90038491 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2681414
TITLE: An IgA monoclonal antibody directed against type III antigen on **group B** streptococci acts as an opsonin.
AUTHOR: **Bohnsack J F**; Hawley M M; Pritchard D G; Egan M L; Shigeoka A O; Yang K D; Hill H R
CORPORATE SOURCE: Department of Pediatrics, University of Utah School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI 13150 (NIAID)
AI 19094 (NIAID)
AI19941 (NIAID)
+
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1989 Nov 15) 143 (10) 3338-42.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198912
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19891215

AB We have investigated the mechanisms by which a murine IgA mAb directed against the type III Ag (IgA anti-III mAb) of **group B** streptococci (**GBS**) protects neonatal rats from lethal infection with these organisms. Purified IgA anti-III mAb enhanced phagocytosis of type III **GBS** by rat peritoneal macrophages in vitro by fourfold compared with phagocytosis of buffer-treated **GBS**. In the absence of antibody, neonatal rat serum did not promote phagocytosis, but addition of neonatal rat serum to **GBS** opsonized with IgA anti-III led to a sevenfold increase in phagocytosis. Heat inactivation of C destroyed the ability of neonatal rat serum to enhance phagocytosis

in the presence of IgA. C3 deposition was observed when **GBS** coated with IgA anti-III mAb were incubated in untreated neonatal rat serum or in serum treated with Mg/EGTA. This latter observation suggested that C3 deposition occurred through activation of the alternative pathway. The control IgA mAb MOPC 315 did not enhance **GBS** ingestion or C3 deposition on **GBS**. Depletion of C in vivo by using cobra venom factor abolished the protective effect of IgA anti-III mAb in the neonatal rat model. These data suggest that the ability of this IgA to activate C further enhances its opsonic activity and may be essential for its protective effect in vivo.

L7 ANSWER 31 OF 32 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 89035480 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3053900
TITLE: **Group B** streptococci inhibit the chemotactic activity of the fifth component of complement.
AUTHOR: Hill H R; **Bohnsack J F**; Morris E Z; Augustine N H; Parker C J; Cleary P P; Wu J T
CORPORATE SOURCE: Department of Pathology, University of Utah, Salt Lake City 84132.
CONTRACT NUMBER: AI13150 (NIAID)
AI19094 (NIAID)
AI20016 (NIAID)
+
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1988 Nov 15) 141 (10) 3551-6.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198812
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881208

AB Infection with **group B** streptococci (**GBS**) is associated with a poor acute inflammatory response in which neutrophils fail to localize at the site of invasion. In the present studies, we have examined the effects of **group B** streptococci on C-derived chemotactic activity in human serum. Fresh human serum was activated to form C5a and C5adesarg by incubation with zymosan. The activated serum was then incubated with **group B** organisms, centrifuged, and the supernatants tested for chemotactic activity for human polymorphonuclear leukocytes. **Group B** organisms caused a dose-dependent decrease in C-dependent chemotactic activity. The degree of inhibition was profound with 1 X 10(9) bacteria/ml (10% of control). Experiments indicated that significant chemotactic factor inactivation occurred within 2 min of exposure to **GBS** organisms, while maximal inhibition occurred after 30 min incubation. A number of different strains of **GBS** of types I, II, and III possessed inhibitory activity. In contrast, group D streptococci, Staphylococcus aureus, Escherichia coli and Klebsiella pneumoniae failed to inhibit the C-derived chemotactic activity in human serum. Group A streptococci that were M protein positive also inactivated C-dependent chemotactic activity in serum, as previously reported. The inhibitory activity of the **GBS** strains could be abolished by

heat or trypsin treatment but not by neuraminidase, pronase, or pepsin. C5a levels in zymosan-activated serum as measured by RIA were not decreased after incubation with an inhibitory strain suggesting that absorption was not involved. SDS-PAGE analysis revealed that **group B** streptococci degrade the C5a molecule, increasing its electrophoretic mobility by removing a fragment with a m.w. of approximately 650 Da. Thus, one of the reasons for the poor inflammatory response at the site of **GBS** infection may reside in the ability of these pathogens to inactivate C-derived inflammatory mediators. The **GBS** C5a-ase activity probably serves as an additional virulence factor for these organisms contributing to the poor inflammatory response characteristic of **group B** streptococcal infection.

L7 ANSWER 32 OF 32 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 89009990 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2844920
TITLE: Effects of fibronectin on the interaction of polymorphonuclear leukocytes with unopsonized and antibody-opsonized bacteria.
AUTHOR: Yang K D; Augustine N H; Gonzalez L A; **Bohnsack J F** ; Hill H R
CORPORATE SOURCE: Department of Pediatrics, University of Utah School of Medicine, Salt Lake City 84132.
CONTRACT NUMBER: AI-13150 (NIAID)
AI-19094 (NIAID)
SOURCE: Journal of infectious diseases, (1988 Oct) 158 (4) 823-30. Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198811
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19980206
Entered Medline: 19881109

AB Fibronectin (Fn) affects the interaction of polymorphonuclear leukocytes (PMNLs) with certain bacteria. Fn alone enhanced the response, in a chemiluminescence (CL) assay, of PMNLs to Staphylococcus aureus (P less than .05) and Staphylococcus epidermidis (P less than .01) but had no effect on type III, **group B** streptococci (**GBS**) or Escherichia coli. When **GBS** or E. coli were first preopsonized in antibody, Fn significantly enhanced the CL response of PMNLs (P less than .05). The intracellular metabolic inhibitor NaN3 but not the extracellular scavengers superoxide dismutase or human serum albumin inhibited Fn-enhanced CL; this fact suggests that enhancement of the respiratory burst by Fn is an intracellular event. We used an acridine orange-crystal violet monolayer assay to examine the effects of Fn on ingestion and intracellular killing of bacteria by PMNLs. Fn alone promoted uptake and killing of S. aureus (P less than .01) and S. epidermidis (P less than .05) by PMNLs but did not enhance monolayer phagocytosis of **GBS** or E. coli, unless these bacteria were preopsonized in antibody (P less than .01).

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Searcher : Shears 571-272-2528